Criteria for use for Leflunomide, Etanercept, and Infliximab in the Treatment of Rheumatoid Arthritis

The following recommendations are dynamic and will be revised, as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

I. FDA approved indications

Leflunomide (Arava®)	1.) Reduction of signs and symptoms of active RA in adults 2.) Retard structural damage as evidenced by x-ray erosions and narrowing of the joint spaces
Etanercept (Enbrel®)	1.) Reduction of signs and symptoms of active RA in adults 2.) Delaying structural damage in patients with moderate-severe active RA, including those who have not previously failed therapy with other DMARDs
Infliximab* (Remicade®)	1.) For combination use with MTX to reduce signs and symptoms of RA in patients with inadequate response to MTX 2.) For combination use with MTX to inhibit progression of structural damage in moderate-severe RA

*infliximab is also approved for Crohn's Disease

II. Criteria for use in VA patients

All patients must have a diagnosis of RA as defined by the American College of Rheumatology

Leflunomide

Documented intolerance to an adequate trial of MTX and failure or intolerance to one to more of the following DMARDs, regardless of whether they were prescribed sequentially or in combination: hydroxychloroquine, oral/injectable gold, sulfasalazine, penicillamine, azathioprine.[1-4]

Preliminary data suggests that patients with an inadequate response to MTX might benefit from combination therapy with leflunomide (one open label study[5] and one abstract[6]). At this time, it may be best to avoid this combination, until more is known if there is an increased risk for liver toxicity.

Etanercept

Documented failure due to lack of efficacy to an adequate trial of MTX and failure or intolerance to one to more of the following DMARDs, regardless of whether they were prescribed sequentially or in combination: cyclosporine, hydroxychloroquine, oral/injectable gold, sulfasalazine, penicillamine, azathioprine, leflunomide. [7-9]

Patients who have satisfied the above criteria and have had a partial but inadequate response to methotrexate, may use etancercept in combination to provide additional benefit.

No single study has looked at whether better outcomes are achieved using MTX + etanercept or using etanercept alone.

One study has looked at the use of etanercept in patients with early rheumatoid arthritis. Because of the prohibitive cost and limited supply, more data is needed before recommending use in these patients.[10]

One study has looked at etanercept in the management of psoriatic arthritis. Lancet 2000:356:385-90

Infliximab
Infliximab has only been studied as add-on therapy to MTX

Documented failure due to lack of efficacy to an adequate trial of MTX and failure or intolerance to one to more of the following DMARDs, regardless of whether they were prescribed sequentially or in combination: cyclosporine, hydroxychloroquine, oral/injectable gold, sulfasalazine, penicillamine, azathioprine, leflunomide.[11-13]

Patients who have satisfied the above criteria and have had partial but inadequate response to methotrexate, may use infliximab in combination to provide additional benefit.

III. Dosage and administration

Leflunomide

1.) Initiate at a loading dose of 100mg per day for 3 days, followed by a maintenance dose of 20mg per day. Response to therapy may be observed within 1-2 months. The dose may be reduced to 10mg daily if the patient is unable to tolerate the 20mg dose.
2.) Dose adjustments for renal insufficiency cannot be recommended at this time due to lack of sufficient information, however, caution should be used since the kidney plays a role in drug elimination.

Etanercept

1.) Etanercept is administered as a subcutaneous injection of 25mg twice weekly, with observed clinical response as early as 1-2 weeks, but more often 2-6 weeks, and maximum response achieved at 3 months. Return of arthritic symptoms has occurred within one month of treatment discontinuation.
2.) Dose adjustments for renal or hepatic impairment cannot be recommended at this time as no formal pharmacokinetic studies have been conducted to examine this effect.
3.) Due to a shortage of etanercept, procedures for drug procurement and patient enrollment are in place.

Infliximab

1.) Initiate at 3mg/kg IV then repeat at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
2.) Reconstitute each vial with 10ml sterile water for injection. Add the total dose of reconstituted infliximab to an IV bag of 250ml of normal saline. Infuse over a period of no less than 2 hours.
3.) For patients who have had an incomplete response with 3mg/kg every 8 weeks, consideration may be given to adjusting the dose to as high as 10mg/kg or treating as often as every 4 weeks.
4.) Dose adjustments for renal insufficiency cannot be recommended at this time due to lack of sufficient information.

IV. Warnings/adverse events

The following post-marketing data on adverse events for infliximab and etanercept was presented at the FDA Arthritis Drugs Advisory Committee on August 17, 2001:

	Remicade (infliximab)	Enbrel (etanercept)
Adverse events reported to the FDA	• Drug taken by an estimated 147,000 patients worldwide • 2300 reported adverse events • 26% of reports related to infection	• Drug taken by an estimated 102,000 patients worldwide • 18,500 reported adverse events • 22% of reports related to infection
Tuberculosis	• 92 cases reported • More than half were in Europe • 77% were taking concomitant immunosuppressives • 14 cases resulted in death • Incidence is estimated as 24 per 100,000 taking Remicade and 6 per 100,000 among RA patients in general	• 5 cases reported worldwide • 2 were in the U.S.
Opportunistic	• 9 reports of histoplasmosis	• 14 cases of opportunistic infections

infections	• 11 reports of listeriosis • 10 reports of Pneumocystis carinii pneumonia	• 5 cases of Pneumocystis where 4 of the patients were receiving concomitant MTX or steroids
Multiple sclerosis		• 17 cases reported • Nneurological panel found no definitive link between etanercept and MS, but urged Immunex to closely monitor all reports
Lymphoma	10 cases reported	18 cases reported

Leflunomide

1. Data from 104,000 patient/years of exposure revealed 129 cases of serious hepatic injury. Two of these patients developed cirrhosis and 15 developed liver failure of which 9 died. Use in patients with hepatic insufficiency is not recommended due to the increased risk of hepatic toxicity, and the need for hepatic metabolism and elimination/recycling of the drug. Do not use in patients with significant liver impairment or who are infected with hepatitis B or C viruses.
2. Avoid use in patients with severe immunodeficiency, bone marrow dysplasia, or severe uncontrolled infections.
3. Leflunomide is **contraindicated** in women who are or may become pregnant. Nursing mothers should not use leflunomide, since it is not known whether the drug is excreted in human milk. Women receiving leflunomide who wish to become pregnant must discontinue leflunomide and undergo the drug elimination procedure. Men wishing to father a child should also consider discontinuation of leflunomide and undergo the drug elimination procedure. (See LFT monitoring).
4. Adverse reactions associated with leflunomide therapy include diarrhea, alopecia, rash, and elevated liver enzymes (See LFT monitoring).
5. Live vaccines should not be given concurrently as there are no data documenting the transmission of infection by live vaccines in patients receiving leflunomide.

Etanercept or infliximab

1. There is a risk of serious infections, including sepsis and death
   - Do NOT initiate in patients with active infections, whether they be acute or chronic, localized or generalized
   - Discontinue if a patient develops a serious infection.
   - Exercise extreme caution in a patient with a history of recurring infections or underlying conditions (such as advanced or poorly controlled diabetes), which predispose them to infections.
   - Infliximab and etanercept have been linked to the development of tuberculosis. Many of the cases with infliximab have occurred within the first 3 infusions. A PPD test should be obtained **PRIOR** to the initiation of these agents. A screening CXR should be obtained for those patients who are receiving chronic immunosuppressants and are PPD negative. If indicated, treatment for active or latent tuberculosis should be started prior to treatment with infliximab or etanercept.
2. Autoantibody development has been reported although clinical symptoms of lupus-like syndrome are rare.
3. Rare cases of demyelinating central nervous system disorders and pancytopenia have been reported with etanercept. Causal relationship to etanercept use is unknown.
4. Injection site reactions with etanercept lasting approximately 3 to 5 days are common in the first month. The frequency of reactions decreases thereafter. Infusion reactions with infliximab have occurred during the infusion or 1-2 hours after the infusion. The incidence of reactions does not increase beyond the first infusion.
5. Etanercept and infliximab have not been studied in pregnant or nursing women, and thus, should not be used during pregnancy or while nursing.
6. Live vaccines should not be given concurrently as there are no data documenting the transmission of infection by live vaccines in patients receiving these agents.

V. Liver Function Test Monitoring for Leflunomide

1. Liver function test (ALT) should be performed at baseline and at monthly intervals during initial therapy. Thereafter, the interval should be determined by the individual clinical situation. Dose adjustment for ALT elevations caused by leflunomide therapy are as follows:
   - ALT>2-fold ULN, reduce dose to 10 mg/day.
   - If ALT persists at >2 but ≤ 3-fold ULN despite dose reduction, liver biopsy should be performed if continued treatment desired.
   - If persistent ALT elevation >3-fold ULN despite cholestyramine administration and dose reduction, discontinue leflunomide and readminister cholestyramine with close monitoring and cholestyramine retreatment as indicated. (Drug elimination procedure below).

2. Drug elimination procedure to achieve nondetectable plasma M1 metabolite levels <0.02mg/L after stopping leflunomide therapy
   - Administer cholestyramine 8g tid for 11 days.
   - Verify plasma levels less than 0.02mg/L by 2 separate tests at least 14 days apart. Additional cholestyramine treatment should be considered if plasma levels are higher than 0.02mg/L.
   - Without this procedure, it may take up to 2 years to reach plasma M1 metabolite levels <0.02mg/L

3. Concurrent use of other medications
   - Increase in side effects may occur with concomitant administration of hepatotoxic substances. Elevation of liver enzymes was observed in 13 of 30 patients receiving a combination of leflunomide and methotrexate, 3 of which met criteria for liver biopsy.
   - Rifampin – Concomitant administration of a single dose of leflunomide and multiple doses of rifampin has resulted in ~40% increase in peak M1 leflunomide levels. Multiple dosing of leflunomide may potentially result in further increases in M1 levels. Therefore, patients receiving both drugs should be monitored for toxicity.

VI. Comparative Cost Information (monthly cost of drug)

These costs represent drug acquisition cost only and do not take into account, IV sets, syringes, lab tests, etc.

Drug	Dose	Price/month
Methotrexate	7.5-15mg/week	$1.78-3.57
Hydroxychoroquine	200mg BID	$8.86
Sulfasalazine EC	500mg QID	$20.66
Gold (Auranofin)	3mg BID	$42.93
Azathioprine	50mg BID	$11.10
Leflunomide	20mg QD	$151.67
Cyclosporine (Neoral/Sandimmune)	100mg BID	$220.02/$244.52
Etanercept	25mg SC twice weekly	$667.30
Infliximab	3mg/kg every 8 weeks	$438.12 (based on using 3 vials)

VII. References

Leflunomide

1. Mladenovic V, Domljan Z, Rozman B, et al. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. Results of a randomized, placebo-controlled, phase II study. Arthritis Rheum 1995; 38:1595-1603.

2. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomized, multicentre trial. Lancet 1999; 353:259-266.

3. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000; 39:655-665.

4. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999; 159:2542-2550.

5. Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999; 42:1322-1328.

6. Kremer JM, Caldwell JR, Cannon GW, et al. The combination of leflunomide and metheotrexate in patients with active rheumatoid arthritis who are failing on methotrexate alone: a double-blind placebo controlled study [abstract]. American College of Rheumatology 64th Annual Scientific Meeting.

Etanercept

7. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997; 337:141-147.

8. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999; 130:478-486.

9. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999; 340:253-259.

10. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000; 343:1586-1593.

11. Genovese M, Martin R, Fleischmann R, et al. Enbrel® (etanercept) versus methotrexate in early rheumatoid arthritis (ERA trial): two-year follow-up [abstract]. American College of Rheumatology 64th Annual Scientific Meeting.

Infliximab

12. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41:1552-1563.

13. Maini R, William St Clair E, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. Lancet 1999; 345:1932-1939.

14. Lipsky PE, van Der Heije D, William St Clair E, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000; 343:1594-1602.